REMARKS

The claims are not amended with this paper. Currently pending in the application are claims 11, 16-20, and 22-35.

Rejections Under 35 U.S.C. § 103

(i) Claims 11, 16-20, 22-26 and 33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yoji et al., in view of Goodman and Gilman, in view of Elkhoury et al. and further view of Ptchelintsev et al. Applicants respectfully disagree and traverse this rejection.

The present invention is directed to methods for topically providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

Yoji purportedly teaches the synergistic effects of morphine and lidocaine or bupivicaine when systemically administered via bolus injection or continuous coinfusion. Yoji does not teach the administration of butamben. Similarly, Yoji does not teach the topical administration of these compounds nor does Yoji suggest that the synergistic effect would be retained in the periphery via topical administration. Yoji does not and cannot render obvious the claimed subject matter by itself, and the Examiner does not allege that Yoji alone renders the claimed subject matter unpatentable.

Despite the statements made in the Office Action, none of the remaining cited references can cure the deficiencies of the Yoji reference. The Office Action cites the Goodman reference as teaching that some local anesthetics have common activities, and that benzocaine and butamben can be applied topically. Applicants have previously pointed out that Goodman also teaches that lidocaine, unlike procaine and benzocaine, is an aminoacetamide (an amide-type anesthetic) and thus will react differently in patients than ester-type anesthetics owing to their different metabolic pathway (hydrolysis via plasma esterase and the liver versus hepatic endoplasmic reticulum). In any event, the Office Action does not suggest that Goodman teaches that a synergistically effective amount of morphine and butamben can be administered to a peripheral site. The Office points to nothing in Goodman that could teach or suggest

that a synergistically effective amount of morphine and butamben can be administered to a peripheral site.

According to the Office Action, Elkhoury teaches the use of morphine for providing topical analgesia. The Office Action concedes that Elkhoury does not teach or suggest the use of butamben. Applicants further point out that Elkhoury lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site.

The Office Action relies on Ptchelintsev as teaching that butamben is a topical analgesic. The Office Action does not allege that Ptchelintsev teaches or suggests the use of morphine. Applicants further point out that Ptchelintsev lacks any suggestion that a synergistically effective amount of morphine and butamben can be administered to a peripheral site.

From the foregoing it can be seen that none of the cited references, whether taken alone or in any combination, teaches or suggest the combination of features of the presently-claimed subject matter, in which a method of providing topical analgesia to a subject includes topically administering to peripheral sites in the subject a pharmaceutical composition comprising (i) synergistically effective amounts of morphine and butamben and (ii) a physiologically acceptable topical excipient, to potentiate analgesia at the peripheral sites.

The Office Action states that it would be obvious to use butamben in the composition of Yoji due to the teachings of Goodman, and that Elkhoury and Ptchelintsev teach that morphine and butamben can be formulated as topical compositions. The Examiner alleges that it would have been logical to combine the teaching of these references given that the analgesic properties were each known individually in the art and their synergistic effect would have been expected. Applicants disagree.

It is respectfully submitted that the topical combination of morphine and butamben in the periphery produces a synergistic result that would have been unexpected to one of skill in the art of pain management at the time the present invention was made. Prior to the teachings of the instant application, the importance of

peripheral mechanisms in the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to be mediated through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. The synergistic potentiation of pain relief that occurs in the periphery when opioid analgesics are administered together with local anesthetics was unexpected given the state of the art.

In fact (as detailed at length in the Response filed August 16, 2007, which is incorporated herein by reference), several medical reports published before the filing of the present application teach that methods comprising the topical use of morphine fail to stimulate peripheral sites. As described previously, the Raja *et al.* (Anesthesiology 77:1143-7; 1992), Rosenstock *et al.* (Ref. Anesth. 21:93-8; 1996), Picard *et al.* (Pain 72:309-18; 1997), and Yarussi et al., (Reg. Anesth. Pain. Med. 24:142-5; 1999) references described various studies in which peripheral analgesia was not seen with morphine.

Further, although the Office Action appears to dismiss the Declaration of Sandra C. Roerig, Ph.D., submitted in related application No. 09/975,812 (now U.S. Patent No. 6,790,855) and discussed in the Response filed August 16, 2007, that Declaration provided evidence that, prior to the invention of the claimed subject matter, scientists did not expect that morphine and lidocaine would synergistically potentiate the antinociceptive effects of each other in the periphery.

For at least the foregoing reasons, there would be no motivation to combine Yoji and/or Goodman with Elkhoury and Ptchelintsev. As discussed above, Elkhoury and Ptchelintsev describe the topical administration of morphine and butamben, respectively. Although the topical anesthetic properties of each of morphine and butamben are disclosed by these references, there is no expectation of their synergistic effect in the periphery. Yoji does not rectify this deficiency as the synergistic effect described systemically by Yoji would not be anticipated when administered topically as

discussed above. Applicants further note that the Examiner's reference (at page 4 of the Office Action) to "many references . . . demonstrating synergy between morphine/lidocaine and morphine/bupivacaine" apparently does not refer to references showing synergy at a peripheral site when administered topically.

The Examiner also states that combining "two compositions . . . useful for the same purpose in order to form a third composition to be use for the very same purpose" is *prima facie* obvious. Even if that were true, a synergistically effective composition would not be *prima facie* obvious. Yoji does not rectify this deficiency, for at least the reason that any synergism of Yoji in systemic administration would not be expected when administered topically to peripheral sites, as discussed above.

Applicants respectfully contend that the Office Action does not even make out a *prima facie* case of obviousness of the present claims.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 is respectfully requested.

Claims 27-32 were rejected under 35 U.S.C. § 103 as being unpatentable over Yoji, Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Mayer et al. Applicants disagree.

Claims 34-35 were rejected under 35 U.S.C. § 103 as being unpatentable over Yoji, Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Soo et al. Again, Applicants disagree.

As stated above, the pending claims are directed to methods for topically providing, to peripheral sites, synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

As discussed in detail above, claims 11-13, 16-26, and 33 are nonobvious in view of the combination of cited references. Claims 27-32 and 34-35 ultimately depend from claim 11. If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the further combination of either Mayer or Soo with the combination of Yoji, Goodman, Elkhoury and Ptchelintsev fails to remedy the deficiencies of those references as described above. The additional references,

whether taken alone or in any combination, cannot render obvious any of the pending claims. Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 is respectfully requested for claims 27-32 and 34-35.

CONCLUSION

Applicants believes the pending application is in condition for allowance. Early and favorable action is earnestly requested.

Applicants conditionally petition for any extension of time necessary for consideration of this response. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 62069DIV2 (51590).

Respectfully submitted,

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